Rifaximin for the Treatment and Prevention of Enteric Infection
Robin McKenzie

Diarrheal diseases are the second leading cause of morbidity and mortality worldwide, causing over 3 million deaths per year, predominantly in young children in developing countries. Among travelers, diarrhea is the most common illness: there are approximately 10 million episodes of travelers' diarrhea each year. Bacteria account for 33-50% of episodes of pediatric diarrhea in developing countries and about 80% of travelers' diarrhea. The most common enteropathogen identified among travelers is *E. coli*.

Rifaximin, a broad-spectrum rifamycin, inhibits RNA synthesis. It is minimally absorbed (<0.4%) and well tolerated. Even when the colon is inflamed, absorption is minimal. Given to volunteers in a *Shigella* challenge study, rifaximin produced peak plasma concentrations and areas under the concentration-time curve that remained similar from day one to day three. Rifaximin has a relatively minor impact on intestinal coliforms, reducing fecal coliforms by about one log. In countries where it has been used for several years, no stable resistance has been reported.

Four field trials evaluated rifaximin as treatment for travelers' diarrhea. Studies conducted in Mexico (72 subjects), Mexico and Jamaica (187 subjects), and Mexico, Kenya, and Guatemala (380 subjects) compared rifaximin to trimethoprim-sulfamethoxazole, ciprofloxacin, and placebo for treatment of travelers' diarrhea. A 3-day course of rifaximin (400 mg twice daily) was comparable to ciprofloxacin in terms of duration of diarrhea after treatment initiation (median, 26 hours vs. 25 hours), and cure rates (87% vs. 88%). Compared to placebo, a 3-day course of rifaximin (200 or 400 mg three times daily) significantly reduced the duration of diarrhea (33 hours for each of the rifaximin groups vs. 60 hours for placebo).

In a fourth (unpublished) randomized, double-blind study, 399 adult travelers to Mexico, Guatemala, India and Peru who developed diarrhea were treated with rifaximin (200 mg three times daily), ciprofloxacin, or placebo. Again the time after treatment initiation until the last unformed stool was comparable for rifaximin (32 hours) and ciprofloxacin (29 hours) and significantly less than for placebo (66 hours). However, subjects with invasive pathogens, (*Campylobacter*, *Shigella*, and *Salmonella*) and those with fever and/or blood in their stools did not respond well to rifaximin probably because invasive bacteria are not susceptible to treatment with a luminal agent.

Since rifaximin is not absorbed but achieves very high luminal concentrations, it is attractive as a potential prophylactic agent for travelers' diarrhea. In a placebo-controlled, double-blind study 210 adults arriving in Mexico were randomized to one of four groups to receive rifaximin (200 mg once, twice or three times daily) or placebo. During the two weeks of the study, 54 % of controls and 15% of rifaximin recipients developed travelers' diarrhea (protective efficacy, 72%). There was no difference in the diarrhea rates for the three different rifaximin doses.

While travelers' diarrhea in Mexico is largely caused by *E. coli*, in some other countries invasive organisms, such as *Shigella* and *Campylobacter*, occur more commonly. Even though rifaximin is not effective for treatment of shigellosis, it may prevent shigellosis by killing the bacteria in the gut lumen before they invade the mucosal epithelium. In a randomized, double-blind trial 15 subjects received rifaximin (200 mg three times daily for 5 days) and 10 received placebo. All were challenged with 1000-1500 cfu of *S. flexneri* 2a. Sixty % of controls but none of the rifaximin-treated subjects developed shigellosis. Furthermore, no one in the rifaximin group became colonized or demonstrated an immune response to the *Shigella* strain, in contrast to the control group, among whom 50% shed the challenge strain, and 80% developed an immune response (serum IgA or IgG or IgA antibody secreting cells).

In conclusion, for treatment of travelers' diarrhea, rifaximin was comparable to ciprofloxacin in efficacy and was most effective for cases caused by *E. coli* and cases for which no pathogen was identified. Rifaximin should not be used for treatment of travelers with fever or blood in their stools since these individuals may have an invasive infection not accessible to a luminal agent. Used for prophylaxis, rifaximin reduced the incidence of travelers' diarrhea from 54% to 15% during a two-week trial in Mexico (72% efficacy). Furthermore, it prevented shigellosis following challenge, probably by eradicating the organisms before invasion. In these studies adverse events were similar to those seen with placebo.

Many questions are raised by these studies. What is the role of rifaximin in treating diarrheal diseases in adult travelers and in children? Would a shorter course (single dose) be effective? Will rifaximin be efficacious for treating enterohemorrhagic *E. coli* and *Clostridium difficile*? What is its role for prophylaxis, and what dose should be used? Will prophylaxis of travelers' diarrhea prevent irritable bowel syndrome? Will resistance to this drug become a problem?